
Subpopulations of human embryonic stem cells with distinct tissue-specific fates can be selected from pluripotent cultures.

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Public Summary:

Scientific Abstract:

Directed differentiation of human embryonic stem cells (hESCs) has generated much interest in the field of regenerative medicine. While subpopulations of hESCs within pluripotent cultures have been identified based on expression of specific surface antigens, their significance and fates are not well understood. To determine whether such subpopulations indicate specific tissue fates or represent stochastic antigen distributions within proliferating cultures, we isolated CD133(+) or CD135(+) hESCs from proliferating cultures constitutively expressing enhanced green fluorescent protein (GFP), and co-cultured these with unselected GFP(-) hESCs. After passage in culture, GFP(+) hESCs reanalyzed for the persistence of CD133 or CD135 expression, as well as other surface antigens (Tra-1-60, SSEA-4, FGFR-1), demonstrated that these two subpopulations continued to express CD133 or CD135 over serial passage, and that CD133(+) hESCs were enriched for SSEA-4 expression as well. Upon differentiation in vitro, CD133(+)GFP(+) hESCs gave rise solely to ectoderm, as detected by expression of nestin. Tissues representing endoderm (alpha-fetoprotein(+)) and mesoderm (smooth muscle actin(+)) were not seen among GFP(+) tissues. In contrast, selection against CD133 gave rise almost exclusively to mesoderm and endoderm. In contrast, CD135(+)GFP(+) hESCs gave rise to tissues representing all three embryonic germ layers, and were virtually indistinguishable from CD135(-)-derived tissues. Similar results were obtained by in vivo differentiation in teratomas. These data establish that subpopulations of proliferating hESCs whose tissue fate is predetermined exist, and challenge the notion that all cells within proliferating hESC cultures are truly "pluripotent." This co-culture approach also will enable identification of other distinct hESC subpopulations, and selection for these should prove valuable in generating tissue-specific reagents for cell-based therapy.

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